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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,485	06/06/2001	Steven Leigh	032553-011	5205

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,485	LEIGH ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 5-14,16-25,27-37 and 39-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 5-14,16-25,27-37 and 39-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims included in the prosecution are 5-14, 16-25, 27-37 and 39-47.

Claim Rejections - 35 USC § 112

1. Claims 5-14, 16-25 and 27-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent claim 31 recites 'in association with a polymer' on lines 4 and 5.

It is unclear whether this expression pertains to all three members of Markush group or only to 'diacyl phospholipids.

It is unclear as to what 'GRAS status' as recited in claim 32 represents.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 5, 7-14, 16-19, 31-39, 42-43 and 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Leigh 5,141,674 of record.

Leigh discloses liposomal powders containing a hydrophobic drug and a lipophilic medium and a polymer such as starch and dextran. The liposomes are made of glycolipids or mono and dialkyl polyoxyethylene derivative or two grades of soybean lecithin (note the abstract, col. 3, line 13 through col. 4, line 25, Example IV and claims).

Leigh's compositions further include a polymer such as starch, dextran, polyethylene and proteins (col.3, lines 61-65). It is known in the art that commercially available lecithins contain lysophospholipids. US 6,303,803, that shows the presence of lysophospholipids, has already been made of record. The examiner also points out that sphingosine (monoacyl compound) containing a sugar residue is a glycolipid.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that in stark contrast to the teachings of Leigh, the polymer associate defined in claims 31, 39 and 43 are made with lipid associates where in the particles each comprise drug/lipid/polymer. The rationale behind this argument is not readily apparent to the examiner since instant claims recite 'lipid--- in association with a polymer' and dependent claims define this polymer to be either a starches, celluloses or gelatins. The expression, 'in association with' does not define the nature of the association and since in Leigh the polymer is in contact with the lipid, it meets instant limitation. With regard to claims 39 and 40, these are product by process claims and therefore, considered as product claims and applicant has not shown that the product is patentably distinct from Leigh's product.

Applicant point out to col. 4, lines 16-17 of Leigh and argues that Leigh requires that the solid carrier must not be soluble in the solvent and therefore, teaches away. This argument is not found to be persuasive since according to claim 39, the organic solvent or organic solvent mixture is removed from a homogeneous *dispersion* containing the polymeric material and according to claim 43, it is 'forming a homogenous *dispersion*' containing the polymeric material (see lines 3 and 4 of claim 43). This indicates that even in instant invention, the solid carrier is not soluble in the solvent.

Applicant while admitting that naturally occurring is known to contain lyso-compounds, argue that these are present only in small quantities and as impurities. This argument is not found to be persuasive since instant claims do not recite any specific

amounts of the lyso compounds and therefore, the prior art preparations which applicant himself admits to contain small amounts of lyso compounds, read on instant claims.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 7-14, 16-19, 23-25, 27-28, 31-33, 35, 39-43 and 46are rejected under 35 U.S.C. 102(a) as being anticipated by Manzo (5,783,211).

Manzo discloses powder formulations containing lecithin (which contains both phosphatidylcholine and lysophosphatidylcholine and polymers such as starches and hydrocolloid gums. The process involves dissolving the phospholipids in a solvent, mixing with a polymer solution and drying (note the abstract, col. 4, line 45 through col. 9, line 5, Examples and claims).

4. Claims 5, 6, 9-10, 12-18, 27-31, 33-37, 44 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 635 218 of record.

EP 218 discloses a freeze-dried product of enzymatically treated lecithin (contains lysolecithin) and a polymeric material (casein). EP also teaches that lysophospholipids are preferable (note the abstract, pages 5-8 and Examples, examples on page 9 and 19 in particular). The compositions are in the form a tablet or a capsule, powders, granules and fine granules (note page 7, lines 53-54).

Claim Rejections - 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 5-14, 16-25, 27-37 and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/26254 in combination with Janoff (4,880,635) and Manzo (5,783,211) cited above.

WO discloses dehydrated liposome compositions containing taxol and monooleoylphosphatidylethanolamine. The formulations can be in the form of tablets for oral administration; according to WO the dehydration is performed according to the method of Janoff (4,880,635) (note the abstract, pages 10, 11, 13, examples and claims). According to Janoff, the dehydration of the liposomes is performed using sugars such as dextrans (col. 5, line 54 et seq.). What are lacking in Janoff are the explicit teachings of the use of the cryoprotectant polymers such as dextrans and those claimed in instant claims and examples showing the dehydration process

Manzo as discussed above, discloses powder formulations containing lecithin (which contains both phosphatidylcholine and lysophosphatidylcholine and polymers such as starches, maltodextrins and hydrocolloid gums. The process involves dissolving the phospholipids in a solvent, mixing with a polymer solution and drying (note the abstract, col. 4, line 45 through col. 9, line 5, Examples and claims). The polymers according to Manzo stabilize the dehydrated compositions.

To dehydrate the formulations of WO in the presence polymers such as those claimed would have been obvious to one of ordinary skill in the art since these are cryoprotective agents as shown by Janoff, and Manzo. The criticality of specific drugs recited in instant claims is not readily apparent to the examiner since liposomes are sustained release agents for any drug and therefore, one of ordinary skill in the art would be motivated to encapsulate any drug with a reasonable expectation of success.

7. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 635 218 cited above, further in view of Manzo cited above.

The teachings of WO have been discussed above. What is lacking in WO is the inclusion of polymers such as polysaccharides and gums. The inclusion of the polysaccharides and gums in WO would have been obvious to one of ordinary skill in the art since Manzo teaches that these compounds provide stability for the solid liposomal compositions.

8. Claims 5-14, 16-19, 31-39, 42-43 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leigh (5,141,674) in view of Huang (5,043,164), Baumann (5,009,956) (all are of record) individually or in combination.

Leigh as pointed out above, discloses liposomal powders containing a polymer and a hydrophobic active agent. The liposomes are also made from two grades of lecithin (note the abstract, col. 3, line 13 through col. 4, line 25, Example IV and claims). Although as pointed out above, Lecithins are known to be impure mixtures of phospholipids including lyso compounds, Leigh does not specifically teach lysophospholipids.

Huang teaches that micelle forming amphiphiles, lysophospholipids stabilize the liposomes (note the claims).

Baumann teaches lysophospholipids prevent liposomal cleavage by phospholipase A and stabilize the liposomes (note the abstract and claims).

The use of lysolipids or the addition of lysolipids in the teachings of Leigh would have been obvious to one of ordinary skill in the art since Huang and Baumann teach the advantages of using the lysolipids. The criticality of specific drugs recited in instant claims is not readily apparent to the examiner since the novelty of the composition rests in the components it would have been obvious to one of ordinary skill in the art to use any drug with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Leigh have been addressed above. Applicant argues that Huang, and Baumann teach that the lysolipids stabilize the liposomes and that the claimed invention however, is not concerned with the formation of liposomes. This argument is not found to be persuasive since applicant's intent to include bilayer structures (liposomes) is clear from the specification on page 5, lines 20-21, page 6, line 32 and page 8, line 32. Furthermore, the motivation to add a lysolipid need not be the same as applicant's. Applicant's arguments that the secondary

references are related to intravenous administration whereas the present invention is substantially related to oral administration are not persuasive since instant claims are product claims and not method of administration claims. With regard to arguments based on the cited references which apparently show that lyso compounds destabilize the liposomes, the examiner points out that the references cited in the rejection show the stability imparted by lyso compounds and the patent office is not equipped to find out whose teachings are right and whose teachings are not. Furthermore, if lyso compounds impart instability then one would expect the same instability of instant compositions also.

9. Claims 5-14, 16-25, 27-37 and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 7291854 (XP-002136413) of record in view of Huang (5,043,164), Baumann (5,009,956) individually or in combination.

JP teaches a method of preparation of a polymeric product containing a drug, a hydrophilic polymer such as a carbohydrate and lecithin using a solvent system, which is either water or water and organic solvent, and drying the product (note the abstract). What is lacking in JP is the use of a lysolipid (monacylphospholipid).

Huang teaches that micelle forming amphiphiles, lysophospholipids stabilize the liposomes (note the claims).

Baumann teaches lysophospholipids prevent liposomal cleavage by phospholipase A and stabilize the liposomes (note the abstract and claims).

The use of lysolipids or the addition of lysolipids in the teachings of JP would have been obvious to one of ordinary skill in the art since Huang and Baumann teach the advantages of using the lysolipids. The criticality of specific drugs recited is unclear since JP is drawn to sparingly soluble drugs and one would expect similar results with any sparingly soluble drug.

Applicant's arguments have been fully considered, but not found to be persuasive. Applicant's arguments with regard to JP are once again based on apparent lack of teachings of the polymer association with the lipids. These arguments have been addressed above. Applicant's arguments with regard to Huang and Baumann have also been addressed above. With regard to lack of mentioning of lecithin in JP abstract, the examiner points out that this reference is submitted by applicant. The rejection will be reconsidered upon the submission of an English translation.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 5-14, 16-25, 31-37 and 39-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim6-36 and 45-46 of U.S. Patent No. 6,599,527. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims recite the same composition in generic terms; one of the members of Markush group recited in the claims of instant application is a combination of monoacyl phospholipid and diacyl

phospholipid. This combination in a specific ratio is claimed in the claims of said patent and therefore, instant claims encompass the limitations in the patented claims.

12. Claims 5-14, 16-25, 31-37 and 39-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-45 and 50-54 of U.S. Patent No. 6,605,298. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims recite the same composition in generic terms; one of the members of Markush group recited in the claims of instant application is a combination of monoacyl phospholipid and diacyl phospholipid. This combination in a specific ratio is claimed in the claims of said patent and therefore, instant claims encompass the limitations in the patented claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is 703 308 2440. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615